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Formalities Officer
Name:
Tel.:

Date
26.10.06

Reference	Application No./Patent No.
N.91525SER	02766997.7 - 2108 / 1432402

Applicant/Proprietor
Celator Pharmaceuticals, Inc.

Decision to grant a European patent pursuant to article 97(2) EPC

Following examination of European patent application No. 02766997.7 a European patent with the title and the supporting documents indicated in the communication pursuant to Rule 51(4) EPC dated 29.05.06 is hereby granted in respect of the designated Contracting States.

Patent No. : 1432402
Date of filing : 03.10.02
Priority claimed : 03.10.01/USP 326671
17.12.01/USP 341529
15.02.02/USP 356759
23.04.02/CAA 2383259
07.08.02/USP 401984
06.09.02/USP 408733

Designated Contracting States and Proprietor(s) : AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR
Celator Pharmaceuticals, Inc.
Floor 2, 1 Airport Place
Princeton, NJ 08540/US

This decision will take effect on the date on which the European Patent Bulletin mentions the grant (Art. 97(4) and (5) EPC).

The mention of the grant will be published in European Patent Bulletin 06/47 of 22.11.06.

Examining Division

Kardas-Llorens E Smeets D Couzy F

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Formalities Officer

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Date
16.10.06

Reference	Application No./Patent No.
N.91525SER	02766997.7 - 2108

Applicant/Proprietor
Celator Pharmaceuticals, Inc.

Notification pursuant to part A-III, 5.3 of the Guidelines for Examination in the EPO

The communication issued pursuant to Rule 17(3) EPC, sent to the inventor designated below, has been returned by the postal services.
You are requested to indicate the correct address of the inventor (R. 17(1) EPC).

Inventor : BALLY, Marcel
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Receiving Section

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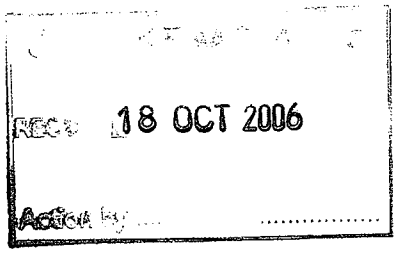

Formalities Officer

Name:

Tel.:

Date
16.10.06

Reference	Application No./Patent No.
N.91525SER	02766997.7 - 2108

Applicant/Proprietor
Celator Pharmaceuticals, Inc.

Notification pursuant to part A-III, 5.3 of the Guidelines for Examination in the EPO

The communication issued pursuant to Rule 17(3) EPC, sent to the inventor designated below, has been returned by the postal services.
You are requested to indicate the correct address of the inventor (R. 17(1) EPC).

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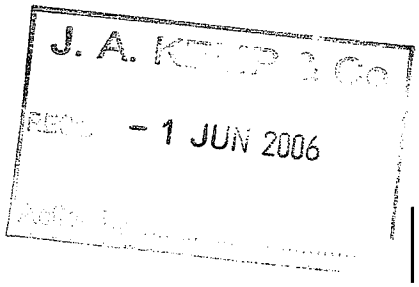

Application No.	Ref.	Date
02 766 997.7 - 2108	N.91525SER	29.05.2006
Applicant: Celator Pharmaceuticals, Inc.		

Communication under Rule 51(4) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

In the text for the Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

Description, Pages

2-7, 11-15, 18-20, 22, 23, 25-29, 32-38, 40-77	as published
1, 8, 9, 9a, 10, 16, 17, 21, 24, 30, 31, 39	received on 11.04.2006 with letter of 11.04.2006

Claims, Numbers

1-5, 6(part), 13-29	received on 25.10.2005 with letter of 21.10.2005
6(part), 7-12	received on 11.04.2006 with letter of 11.04.2006

Drawings, Sheets

1/34-34/34	as published

A copy of relevant documents is enclosed

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name of the applicant and the bibliographic data are shown on the attached EPO Form 2056.

Registered Letter
EPO Form 2004 01.06CSX

You are requested within a **non-extendable** period of four months of notification of this communication

1. to file 1 set of translations of the claim(s) in the two other EPO official languages;

		EUR
2a. to pay the fee for grant including the fee for printing up to and including 35 pages;	Reference 007	750.00
2b. to pay the printing fee for the 36th and each additional page; number of pages: 85	Reference 008	935.00
3. to pay the additional claim fee(s) (Rule 51(7) EPC); number of claims fees payable:	Reference 016	0.00
	Total amount	1685.00

Concerning the possibility of a request for accelerated grant pursuant to Article 97(6) EPC, reference is made to OJ EPO 2001, 459.

If you do not approve the text intended for grant but wish to request amendments or corrections, the procedure described in Rule 51(5) EPC is to be followed.

If this communication is based upon an auxiliary request, and you reply within the time limit set that you maintain the main or a higher ranking request which is not allowable, the application will be refused (Article 97(1) EPC, see also Legal Advice 15/05 (rev. 02), OJ 6/2005, 357).

If the enclosed claims contain amendments proposed by the Examining Division, and you reply within the time limit set that you cannot accept these amendments, refusal of the application under Article 97(1) EPC would result in the case that agreement cannot be reached on the text for grant.

In all cases except those of the previous two paragraphs, if the grant, printing or claims fees are not paid, or the translations not filed, in due time, the European patent application will be deemed to be withdrawn (Rule 51(8) EPC).

For all payments you are requested to use EPO Form 1010 or to refer to the relevant reference number.

After publication, the European patent specification can be downloaded free of charge from the EPO publication server https://publications.european-patent-office.org or ordered only from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Upon request in writing each proprietor will receive the certificate for the European patent **together with one copy** of the patent specification only if the request is filed within the time limit of Rule 51(4) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 51(4) EPC. The requested copy is free of charge. If the request is filed after expiry of the Rule 51(4) EPC time limit, the certificate will be delivered without a copy of the patent specification.

Translation of the priority document(s)

If the translation of the priority document(s), as required by Article 88(1) EPC, or the declaration according to Rule 38(5) EPC has not yet been filed, Form 2530 will be despatched separately. The translation is to be filed within the above mentioned time limit (Rule 38(5) EPC).

Note on payment of renewal fees

If a renewal fee falls due between notification of the present communication and the proposed date of publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (Rule 51(9) EPC).

Under Article 86(4) EPC, renewal fees are payable to the European Patent Office until the year in which the mention of the grant of the European patent is published.

Filing of translations in the Contracting States

Pursuant to Article 65(1) EPC the following Contracting States require a translation of the specification of the European patent in their/one of their official language(s) (Rule 51(10) EPC), **insofar** this specification will not be published in their/one of their official language(s)

- within **three** months of publication of the mention of such decision:

AT	AUSTRIA	FI	FINLAND
BE	BELGIUM	FR	FRANCE
BG	BULGARIA	GB	UNITED KINGDOM
CH	SWITZERLAND / LIECHTENSTEIN	GR	GREECE
CY	CYPRUS	IT	ITALY
CZ	CZECH REPUBLIC	NL	NETHERLANDS
DE	GERMANY	PT	PORTUGAL
DK	DENMARK	SE	SWEDEN
EE	ESTONIA	SK	SLOVAKIA
ES	SPAIN	TR	TURKEY

- within **six** months of publication of the mention of such decision:

IE IRELAND

The date on which the European Patent Bulletin publishes the mention of the grant of the European patent will be indicated in the decision on the grant of the European patent (EPO Form 2006).

The translation must be filed with the national Patent Offices of the Contracting or Extension States in accordance with the provisions applying thereto in the State concerned. Further details (e.g. appointment of a national representative or indication of an address for service within the country) are given in the EPO information brochure "National law relating to the EPC", and in the supplementary information published in the Official Journal of the EPO, or available on the EPO website.

Failure to supply such translation to the Contracting and Extension States in time and in accordance with the requirements may result in the patent being deemed to be void ab initio in the State concerned.

Note to users of the automatic debiting procedure

Unless the EPO receives prior instructions to the contrary, the fee(s) will be debited on the last day of the period of payment. For further details see the Arrangements for the automatic debiting procedure (see Supplement to OJ EPO 2, 2002).

Examining Division:

Chairman:	Couzy, F
2nd Examiner:	Smeets, D
1st Examiner:	Kardas-Llorens, E

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Enclosure(s): Form 2056
120 Copies of the relevant documents

Registered Letter
EPO Form 2004 01.06GSX

ADDITIONAL SHEET +++ IMPORTANT INFORMATION +++

1. **For communications under Rule 51(4) EPC issued on or after 01.04.2005 the time limit of four months is not extendable anymore:**

   According to Rule 51(4) EPC as amended the time limit set in the communication under Rule 51(4) EPC will be four months in all applications without possibility of extension.

   Amended Rule 51(4) EPC applies to all applications for which a communication under Rule 51(4) EPC is issued on or after 01.04.2005.

2. **A copy of the patent specification will only be annexed to the European Patent certificate upon special request within the time limit of the 51(4) EPC communication:**

   Under Rule 54 EPC as amended and the decision of the President of the EPO dated 22.12.2004 (OJ EPO 2005, 122) each proprietor will receive the certificate for the European patent together with a copy of the patent specification upon request in writing and only if the request is filed within the time limit of Rule 51(4) EPC. If such request has been previously filed, it has to be confirmed within the time limit of Rule 51(4) EPC. The requested copy is free of charge.

   If the request is filed after expiry of the Rule 51(4) EPC time limit, the certificate will be delivered without a copy of the patent specification.

   After publication, the European patent specification can be downloaded free of charge from the EPO publication server https://publications.european-patent-office.org or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

   As before, upon payment of an administrative fee a duplicate copy of the European patent certificate with the patent specification attached or a certified copy of the patent specification will also be supplied.

Annex to EPO Form 2004, Communication under Rule 51(4) EPC

Bibliographical data of European patent application No. 02 766 997.7

For the intended grant of a European patent, the bibliographical data are set out below, for information:

Title of invention:

- ZUSAMMENSETZUNGEN ZUR VERABREICHUNG VON ARZNEIMITTELKOMBINATIONEN
- COMPOSITIONS FOR DELIVERY OF DRUG COMBINATIONS
- COMPOSITIONS POUR L'ADMINISTRATION DE COMBINAISONS MEDICINALES

Classification: INV. A61K9/00

Date of filing: 03.10.2002

Priority claimed:

US / 03.10.2001 / USP326671
US / 17.12.2001 / USP341529
US / 15.02.2002 / USP356759
CA / 23.04.2002 / CAA2383529
US / 07.08.2002 / USP401984
US / 06.09.2002 / USP408733

Contracting States* for which fees have been paid:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

Extension States* for which fees have been paid:

Applicant(s):**

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*)	In case the time limits pursuant to Article 79(2) and Rule 85a EPC have not yet expired, **all Contracting States/Extension States** have been mentioned.
**)	In case two or more applicants have designated different Contracting States, this is indicated here.

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BY HAND

The European Patent Office
Erhardtstrasse 27
D-80469 Munich
Germany

28 March 2006

Dear Sirs

European Patent Application No. 02766997.7-2114
CELATOR PHARMACEUTICALS, INC.
Our Ref : N.91525 SER/mr

I refer to the summons to Oral Proceedings issued 20 December 2005. I set out the final written submissions of the Applicant pursuant to Rule 71a EPC. I am filing herewith a new Main Request and First and Second Auxiliary Requests which are discussed in more detail below. The Applicant trusts that in the light of the new Main Request being filed at this time and the detailed submissions set out below, the Examiner will be in a position to allow this application without the need for the Oral Proceedings currently set for 28 April 2006. If the Examiner is minded to allow one of the claim requests being filed at this time, or has some further minor issues to be addressed, he is invited to telephone the undersigned so that, if possible, this matter may be resolved without the need for the Oral Proceedings on 28 April 2006. However, if the Examiner is not minded to accept any of the Requests, we maintain our request for Oral Proceedings.

In the event that the Oral Proceedings scheduled for 28 April 2006 do take place, I will be accompanied at the Oral Proceedings by Kate Murashige, Dr Andrew Janoff and Dr Lawrence Mayer.

I am filing herewith:
- retyped claims of a new Main Request and First and Second Auxiliary Requests;
- a manuscript amended version of the claims as currently on file showing the amendments being made to reach the claims of each Request;
- an Annex setting out the basis for the amended claims of each Request;
- Declaration of Professor Sartorelli, referred to herein as D12;
- Declaration of Professor Bertino, referred to herein as D13;

- Declaration of Professor Hait, referred to herein as D14;
- Declaration of Professor Lazo, referred to herein as D15;
- Saltz et al, J. of Clin. Oncology Vol. 14, No. 11, 1996, pages 2959-2967, D16;
- Cancer Treatment, Fifth Edition, 2001, Chapter 8, D17;
- Cancer : Principles and Practice of Oncology, Fifth Edition, Chapter 17, D18;
- Declaration of Dr Mayer referred to herein as D19;
- An abstract summarising a phase I clinical trial in accordance with the present invention, D20.

Claim 1 of the Main Request

In the Main Request, the Examiner will see that claim 1 has been limited to a pharmaceutical composition for parenteral administration. The pharmaceutical composition comprises particulate delivery vehicles. The first and second therapeutic agents have been defined as antineoplastic agents. Finally, the first and second agents are said to be associated with the delivery vehicles to maintain a non antagonistic ratio in the blood on administration. This claim is closely based on claim 2 as originally filed.

Claim 1 of the Main Request as now on file emphasises a key feature of the present invention namely that a non-antagonistic ratio of the drugs is maintained on administration. We refer for example to paragraph 19 of the specification which emphasises the importance of administration such that a non-antagonistic ratio is maintained at the disease site. As is explained in paragraph 129, the drug to drug ratio determined in the blood is comparable to the drug to drug ratio in the extravascular space. Since it would be more usual to determine the drug to drug ratio in the blood rather than from a tumor sample, specific reference to the blood has been incorporated into claim 1.

A wide variety of different ways in which this could be achieved is described in the present application. We refer, for example, to paragraph 75 which indicates that the non-antagonistic ratio may be maintained by co-encapsulation of the agents in vehicles or by selection of delivery vehicles to control the pharmacokinetics of the composition to maintain the non-antagonistic drug ratio. A wide variety of particulate delivery vehicles are described in the specification, see for example paragraph 71. Pharmacokinetic control via parenteral drug delivery vehicles, such as nanoparticles, micelles and derivatised single chain polymers, has been utilised widely for individual agents. Thus, the present application teaches one of skill in the art to select vehicles appropriate to control the pharmacokinetics of the composition. This is a matter of routine to one of skill in the art to select appropriate delivery vehicles to obtain a pharmaceutical composition as now claimed.

We also refer to paragraph 19 of the specification which emphasises the importance of administration such that non-antagonistic ratios are maintained at the disease site. As is explained in paragraph 129, the drug to drug ratio determined in the blood is comparable to the drug to drug ratio in the extravascular space.

The present invention

Before addressing the individual objections raised by the Examiner, it may be helpful to consider the nature of the present invention and the background prior art at the time that the present application was filed.

The present inventors have identified that maintaining a non-antagonistic drug to drug ratio is important and desirable for the administration of a combination of drugs. The present inventors teach a number of different ways in which the drugs may be associated with particulate delivery vehicles such that this ratio is maintained. This is a key distinction over the prior art where no steps have been taken by those of skill in the art to maintain the drug to drug ratio.

The prior art cited by the Examiner can be split into two separate categories namely those documents which are concerned with *in vivo* administration of combinations of drugs and those documents which look at the interaction of a combination of drugs *in vitro*, to determine whether there is antagonism or non-antagonism. While the *in vitro* studies can be said to show that those of skill in the art appreciated that the antagonistic or non-antagonistic effect of two drugs *in vitro* was dependent on the ratio of those two drugs, this information has not been applied by those of skill in the art when producing a pharmaceutical composition for *in vivo* delivery. In contrast, those studies which are carried out *in vivo* look for the maximum tolerated dose of each drug individually when used in combination, without any consideration of the drug-drug ratio. Indeed, a review of the *in vivo* studies demonstrates that the maximum tolerated dose of each drug is determined without any consideration of the ratio of the two drugs that are being administered, let alone any suggestion that the two drugs should be associated with delivery vehicles in order to maintain a desired ratio.

We are filing herewith four declarations (D12 to D15) from those of skill in the art which clearly demonstrate the significance of the advance made by the present invention. For example, turning to D12 Professor Sartorelli states that the invention:

> *"provides a breakthrough in the compositions used to administer combination therapy".*

Professor Sartorelli summarises the state of the art in paragraph 5 of his declaration. He acknowledges that *in vitro* studies are being carried out but also states that:

> *"no one thought of using such techniques to control the ratio of combination drugs in vivo".*

In paragraph 7, Professor Sartorelli goes on to state:

> *"by taking this step, a combination of drugs that had shown modest effectiveness in the clinic was made dramatically more effective".*

Professor Bertino also discusses the present invention, referred to as the CombiPlex™ approach in his declaration, D13. In paragraph 3 of his declaration, Professor Bertino states:

> *"To my knowledge, the CombiPlex™ approach is the first time the problem of maintaining non-antagonistic ratios of drugs in combination has been recognised or any solution attempted".*

In paragraph 4, Professor Bertino goes on to state:

> *"In my opinion, achieving this result and solving the problem of differing metabolic fates and pharmacokinetics of drugs in combination is important and significant".*

Dr Hait also discusses the present invention, referred to as CombiPlex™ Technology in his declaration D14. In paragraph 3 of his declaration, he states:

> *"I have never encountered a product that takes advantage of the ratios of drugs that have been determined to be synergistic in vitro so as to fix this ratio in a manner that it is maintained in vivo".*

In paragraph 4 of his declaration, he states:

> *"At first, I was as sceptical as the next person about the significance of the CombiPlex™ concept. However, when I reviewed the data obtained in animals showing that indeed constant ratios could be maintained and synergistic effects realised, I realised that this was a potential advance of great significance."*

This initial scepticism and then realisation of the significant advance provided by the present inventors is also discussed in the declaration of Professor Lazo, D15. In paragraph 2 of his declaration, Professor Lazo states:

> *"When the concept was first described to me, I dismissed it as uninteresting and declined to serve on the board."*

Professor Lazo goes on to state in paragraph of this declaration:

> *"I was converted from a non-believer into a believer. It was apparent that this concept filled a serious gap in the approach being taken to combination therapies by the clinical community".*

In paragraph 5 of the his declaration, Professor Lazo goes on to describe the traditional approach that is used to determine the dosages of drugs that are used in combination therapies. This general approach is borne out by a review of the references cited by the Examiner dealt with in more detail

below.

Thus, these declarations demonstrate that those of skill in the art and the field consider that the present invention has made a significant contribution to the state of the art.

The State of the Art - *in vitro* studies

To illustrate the comments made above, we refer to the documents cited by the Examiner. D1, D5, D8 and D11 all relate to *in vitro* studies. Turning in more detail to the disclosure of D1, a synergistic combination is identified *in vitro*. However this synergism is dependent on the dosing schedule. In the final paragraph of D1, the authors question how this information can be used for *in vivo* use, and refer to the work presented in reference 33, that is Saltz et al., Journal of Clinical Oncology, Vol. 14, No. 11 1996, pages 2959-2967, a copy of which is attached as D16. The relevance of this document is discussed below together with the other *in vivo* references. The disclosure of D5 is similar to that of D1.

D8 and D11 are similar, describing studies of various drug combinations on cell lines. These studies could be used in accordance with the present invention to decide on the ratios desirable for combinations of drugs. In each of the studies set out in D8 and D11, the compositions are not administered *in vivo*. D11 discusses in the final paragraph the application of these *in vitro* studies to *in vivo* results. In particular, the authors state:

> *"However, the question of how far these results can be applied to human conditions in vivo remains unanswered".*

The State of the Art - *in vivo* studies

To consider how one of skill in the art might apply the teaching of *in vitro* studies when administering drugs *in vivo*, we can look at the other documents cited by the Examiner namely D2, D3, D4, D6, D7, D9, D10 and the Saltz et al reference referred to above and filed herewith as D16.

Turning firstly to the Saltz et al reference, the document is particularly concerned with identifying the maximum-tolerable dose of 5FU when given with fixed doses of leucovorin and irinotecan. All drugs were given by intravenous injection, see right hand column on page 2959. The authors did not take any steps to consider the ratio of the drugs that was being administered and certainly there is no suggestion that the administration of the drugs is controlled by the use of particulate delivery vehicles so that such a ratio is maintained on administration. Indeed, the only criteria that the authors used was to increase the individual doses of one drug whilst fixing the dose of a second drug to find the maximum-tolerable dose of each drug.

D2 reviews a number of studies of different drug combinations which include gemcitabine. In each case, it can be seen that the dosages of the individual drugs were altered in response to any toxic

effects that were seen. There is clearly no suggestion in this document that a ratio of drugs is established and that the pharmaceutical composition is formulated in order to maintain that ratio on administration. In the majority of cases in D2, particulate delivery vehicles are not used and in general, separate compositions were injected, the dose of each composition individually being altered in response to any toxic effects. Clearly, altering the dose of one drug without altering the dose of the other will change the ratio of these drugs.

D3 describes a new class of anti-tumor agent designated cryptophycins. These agents are first administered to identify the maximal tolerated doses, see page 1266 passage bridging left and right hand column. The authors then looked at a number of different combination treatments, the majority of which require sequential administration of two agents. No consideration is given to the ratio of the two drugs being administered or any suggestion that such a ratio should be maintained on administration. Page 1267 left hand column final paragraph confirms that each chemotherapeutic agent was administered on a standard dosage regimen.

D4 is a review article looking specifically at CPT-11 (irinotecan). This document summarises a number of prior art disclosures looking at the results of clinical studies such as those set out in Saltz et al referred to in more detail above.

D6 describes clinical trials in which individual compositions of irinotecan and cisplatin are administered to individuals. Page 27 right hand column confirms that the doses of each individual agent are selected to be the maximum tolerated doses. As highlighted above in relation to the discussion of Saltz et al, such doses are determined by fixing the dose of one drug and increasing the dose of the second drug to establish the maximum tolerated dose.

The disclosure of D7 is similar to that of D6, and refers expressly to dose limiting toxicity and identification of a maximum tolerated dose. This is determined for the two agents individually by fixing the dose of one drug and increasing the dose of the other. Clearly, therefore the ratio of the two drugs is not under consideration.

D9 is a study looking at arrythmias associated with chemotherapeutic combinations. No specific information is provided relating to the dosages of the individual drugs that are used in the study other than to specify the doses used. The drugs are generally administered separately and based on the general disclosure in the field, it can be assumed that the ratios of the drugs are not considered .

D10 relates to the use of a high dose of carboplatin. A general reference is given to the use of carboplatin in combination with a variety of other agents. However, no specific information is provided relating to the dosages used.

In summary, it can be seen that the prior art using combinations of drugs identifies the maximum tolerated dose of each drug individually. Usually, this is established by fixing the dose of one of the drugs whilst increasing the dose of the other drug to identify the maximum tolerated dose and

repeating so that the maximum tolerated dose for each drug is determined. The drugs are usually administered independently of each other.

The fact that those of skill in the art routinely identify the dose of each drug to be used in a combination without regard to the ratio of the drugs can be further illustrated by looking at standard text books in the field of combination chemotherapy. For example, we are filing herewith chapter 8 of Cancer Treatment, Fifth Edition 2001, D17. The section on page 80 deals with combination chemotherapy. The principles of the design of such combinations are summarised. Point 3 states as follows:

> *"Drugs that are chosen generally have different toxic side effects, allowing the administration of full or nearly full doses of each of the active agents."*

Thus, this text book confirms that the dosage levels are designed by administering as close to the maximum tolerated dose of each drug. Clearly, this approach does not consider the ultimate ratio of the two drugs that is administered let alone whether this ratio is intended to be maintained on administration.

Similarly, the same principles can be found in an earlier text book namely Cancer: Principles and Practice of Oncology, Fifth Edition, Chapter 17, a copy of which is also enclosed as D18. The principles governing the use of combination of drugs are discussed in the sections on pages 335-337. The principles to be followed are set out in the left hand column of page 336. Again, there is no discussion whatsoever in this text book relating to the relationship between the ratio of the drugs and their efficacy in combination nor any suggestion that this ratio needs to be maintained.

The ratio cannot be maintained simply by administering the drugs without associating them with particulate vehicles. Because drugs are metabolised differently when administered as a free drug cocktail, their ratio in the blood after they have been administered to a subject will very quickly be altered. Even if a non-antagonistic ratio is injected, the concentration of one of the drugs in the blood will diminish much faster than the other and the ratio as administered is drastically altered. However, by using the particulate delivery vehicles of the present application, for example by co-encapsulating the drugs or by injecting mixtures of particles associated with each drug, it is possible to maintain a non-antagonistic ratio.

We are filing herewith a declaration by Dr Mayer, referred to herein as D19. As the declaration of Dr Mayer shows, when a free drug cocktail of two drugs namely irinotecan and floxuridine is administered to mice, the injected ratio is immediately altered to an antagonistic one. However, the Examples in the present patent demonstrate that the pharmaceutical compositions according to the present invention allow for a non-antagonistic ratio to be maintained. Example 5, and in particular paragraph 184 referring to Figure 8, confirms that a non-antagonistic ratio was maintained. Example 8 at paragraph 203 provides an alternative route to maintain a non-antagonistic ratio. Examples 22 and 23, which use the same combination of drugs that are shown in the declaration of

Dr Mayer, confirm the enhanced efficacy of the drugs when formulated in accordance with the present invention.

There is no suggestion in any of the prior art documents that a pharmaceutical composition should be formulated which comprises particulate delivery vehicles having associated therewith the first and second drugs wherein the mole ratio is selected to exhibit a non-antagonistic effect and wherein the first and second agent are associated with the delivery vehicles to maintain a non-antagonistic ratio on administration. It is quite clear from a review of the art that while *in vitro* studies may have been carried out to identify synergistic or non-antagonistic ratios, this teaching is effectively ignored in the formulation and dosing of pharmaceutical compositions when delivered to an individual. It had not previously been considered by any one of skill in the art to use the ratios identified *in vitro* and to formulate the pharmaceutical composition such that this ratio was maintained on delivery to a patient. Thus, it is quite clear that the present invention represents a significant departure from the conventional teaching in this field. The declarations that are being filed at this time clearly confirm that the present invention represents a completely new approach. Furthermore, compositions in accordance with the present invention have been demonstrated to be effective.

In more detail, a pharmaceutical composition in accordance with the present invention has now been progressed to a phase 1 study. We attach an abstract which records the results of this study as D20. These studies are discussed in the declarations of Professor Sartorelli, Professor Bertino, Dr. Hait. and Professor Lazo, D12 to D15. For example, Professor Sartorelli stated that, by formulating a combination of drugs in accordance with the invention,:

> *" a combination of drugs that had shown modest effectiveness in the clinic was dramatically more effective"*

even though the patients

> *"had essentially no hope of recovery"*

and the treatment

> *"would be expected to have minimal therapeutic effect."*

<u>The objections raised in the summons to Oral Proceedings</u>

Turning now to the specific objections raised by the Examiner in the summons to Oral Proceedings, the Examiner's objections relating to clarity were particularly concerned with the reference to "stably associated". We trust that in the light of the amendments made to the claims, the Examiner's objections have been overcome. The claims have been amended to make it clear that the first and second antineoplastic agents are associated with particulate delivery vehicles at a non-antagonistic ratio and that the association is such that the first and second agents are maintained at a

non-antagonistic ratio on administration to an individual.

The specification describes a variety of different ways in which the desired ratio of drug can be maintained on administration *in vivo*. A number of different particulate delivery vehicles are described, see for example paragraph 71 of the present application. Paragraph 75 confirms that the non-antagonistic ratio may be maintained by co-encapsulation of the agents in vehicles or by selection of separate delivery vehicles to control the pharmacokinetics of the composition to maintain the non-antagonistic drug ratios.

Such pharmacokinetic control via parenteral drug delivery vehicles such as nanoparticles, micelles and derivatised single chain polymers has been utilised widely for individual agents. Thus, once one of skill in the art has been taught, in accordance with the present invention, to select vehicles appropriate to control the pharmacokinetics of the composition, it is then a matter of routine to select the appropriate delivery vehicles to obtain a pharmaceutical composition as now claimed. Claim 1 of the Main Request has been clarified so that the reference to "stable association" incorporates the alternative language provided in paragraph 70, namely that the agents remain associated with the delivery vehicle at a non-antagonistic ratio on administration to the subject.

The Examiner had previously construed the claims to include particles that might occur in tablets to be administered orally. The claims have now been limited to specify that the composition is for parenteral administration. Thus, the claims clearly no longer encompass tablets for oral administration. The claims require the presence of particulate delivery vehicles, and as has been explained above, the claims have been further amended to specify that the first and second agents are associated with the delivery vehicles to maintain non-antagonistic ratios of the drug on administration. Clearly, this would not occur in a tablet for oral administration.

In the summons, the Examiner has suggested that the present invention can be defined by technical terms and are not necessarily only functional. However, the Examiner has not provided any guidance to indicate in what way he considers that the claims might be more clearly defined.

The Guidelines at CIII 4.7 states that a definition that can be regarded as a result to be achieved can be allowed and in particular states that this:

> *"may be allowed if the invention either can only defined in such terms or cannot otherwise be defined more precisely without unduly restricting the scope of the claims and if the result is one which can be directed and positively verified by test or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation".*

This is clearly the case here. The function of the delivery vehicles is to maintain the ratio as non-antagonistic when the tumor is targeted. This can be achieved in a wide variety of different ways depending on the nature of the drugs being used in the combination and the nature of the particulate

delivery vehicles. A wide variety of different particulate delivery vehicles are described in the specification. As specified in paragraph 75, this could be achieved by simple co-encapsulation, but could also be controlled by taking into account the pharmacokinetics of the delivery vehicle and the drug to be administered. Knowledge of pharmacokinetics of delivery vehicles and drugs to be administered is clearly a matter of routine knowledge to one of skill in the art. However, the selection of an appropriate delivery vehicle will be different for each drug combination.

To define these terms more precisely would unduly restrict the scope of the claims since there would need to be a different claim for each and every composition. The result to be achieved can however be directly and positively verified by tests that would be available to one of skill in the art. As is set out in the specification, it is readily possible to verify the ratio of the drugs that occurs in the blood to establish whether non-antagonism has been maintained.

The Examiner has indicated that Decision T68/85 is not considered to be applicable to the present application although it is not clear why this is the case. The Guidelines themselves cite Decision T68/85. The claim of concern in that Decision referred to "in a quantity producing a synergistic herbicidal effect". As stated in paragraph 8.4.4 of T68/85:

> *"Moreover, the skilled person is given precise directions - should he need them - as to how he can by means of various tests (Colby method) recognise and even calculate a synergistic effect ... while the tests take a long time ... the effort called for on the part of the skilled person must be regarded as reasonable".*

In the present case, detailed tests are provided for determining non-antagonistic ratios *in vitro*. Tests that could be performed on tumor cell lines or cultures using the sample obtained from the subject are set forth in paragraphs 92 and 93 of the present application. The ratio itself can be determined, for example using standard chromatographic means.

The use of a functional definition in former claim 1 was also criticised by the Examiner. This functional definition related to testing for a non-antagonistic effect over 5% of the concentration range where more than 1% of the cells are affected. This too is permitted by the Guidelines. Functional definitions are governed by C-III 6.5 which states that :

> *"A claim may broadly define a feature in terms of its function ... even where only one example of the feature has been given in the description if the skilled reader would appreciate that other means could be used for the same function."*

This is clearly the case in the present application. The Applicant has provided detailed explanations of how to obtain the desired function, by adjusting ratios until the required non-antagonism over the desired range is found. A variety of different ways are provided in order to formulate the compositions to maintain this desired ratio.

A number of ways to determine non-antagonism has been set out in the specification. The Chou-Talalay method of determining non-antagonism as a function of concentration has been exemplified. It is explicitly stated at paragraph 82 of the present application that:

> *"determination of ratios of agents that display synergistic or additive combination effects over concentration ranges may be carried out using various algorithms based on the types of experimental data described below".*

Thus, although the commercially available Chou-Talalay method is exemplified, any method to obtain this result could be used.

The Examiner has not raised any specific objections of lack of novelty or inventive step in the summons to Oral Proceedings but merely refers to the objections that were previously raised. These were of course dealt with in detail in our response of 21 October 2005.

The Examiner had cited D1, D2 and D7 as being novelty destroying for the claims. As explained in our letter of 21 October 2005 and discussed in some detail above, D1 only relates to studies *in vitro*. Each of the drugs are administered in solution and not in the presence of any particulate delivery vehicle. There is no discussion in this document as to how a pharmaceutical composition should be formulated and certainly no suggestion that a pharmaceutical composition should be formulated comprising particulate delivery vehicles in which the first and second agents are present in a non-antagonistic ratio and are associated with the delivery vehicles to maintain that ratio on administration *in vivo*.

D2 cited by the Examiner does not appear to be prior art since it was not published until after the priority date of the present application. In any event, as has also been explained in some detail above, the disclosures of D2 and D7 are primarily concerned with a combination of agents in which the maximum tolerated dose of each agent is identified independently. There is no suggestion in this document that the ratios of the drug should be selected to be non-antagonistic let alone that the pharmaceutical compositions are formulated with particulate delivery vehicles to maintain their non-antagonistic ratio on administration.

Finally, the Examiner has indicated that the wording of the first medical use claim according to claim 27 needs to be discussed. Claim 27 is in a standard format for a first medical use claim. However, if the Examiner has any specific objection to the wording of this claim, he is invited to telephone the undersigned to expand on the nature of the objection so that this can be addressed.

We trust that in the light of these submissions, the Examiner is in a position to acknowledge that the claims of the Main Request would form a basis for allowance. Should the Examiner be minded to reject the Main Request, we request that the application proceed on the basis of the First or Second Auxiliary Request being filed at this time. In the event that it should prove necessary, we request that a further opportunity be provided to file additional Auxiliary Requests. We believe that the

amendments made in the First and Second Auxiliary Requests are clear and no further explanation is required at this time in relation to the amendments that have been made.

We trust that this takes care of all of the issues arising in the summons to Oral Proceedings. As highlighted above, the Applicant invites the Examiner to telephone the undersigned should there be any further issues arising. The undersigned will endeavour to telephone the Examiner within the next week or so to clarify any issues that might still be arising in the hope that the issues can be resolved by telephone so that the Oral Proceedings can be cancelled.

Please acknowledge receipt of this letter by date stamping and returning the enclosed acknowledgement copy.

Yours faithfully

SARAH E. ROQUES

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REC'D - 5 JAN 2006
Action by

Formalities Officer
Name:
Tel.:

Date 02.01.06

Reference	Application No./Patent No.
N.91525SER	02766997.7 - 2114

Applicant/Proprietor
Celator Pharmaceuticals, Inc.

Communication

concerning the registration of amendments relating to

☑ a transfer (Rules 20 and 61 EPC)

☐ entries pertaining to the applicant/the proprietor (Rule 92(1)(f) EPC)

As requested, the entries pertaining to the applicant of the above-mentioned European patent application / to the proprietor of the above-mentioned European patent have been amended to the following:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR
Celator Pharmaceuticals, Inc.
Floor 2, 1 Airport Place
Princeton, NJ 08540/US

The registration of the changes has taken effect on 20.12.05.

In the case of a published application/a patent, the change will be recorded in the Register of European Patents and published in the European Patent Bulletin (Section I.12/II.12).

Your attention is drawn to the fact that, in the case of the registration of a transfer, any automatic debit order only ceases to be effective from the date of its express revocation (cf. point 14(c) of the Arrangements for the automatic debiting procedure, Supplement to OJ EPO 2/2002).

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Nielsen-Hannerup, tel: 7739

Date 20-12-2005

Reference	Application No./Patent No.
N.91525SER	02766997.7 - 2114

Applicant/Proprietor
Celator Technologies Inc.

Summons to attend oral proceedings pursuant to Rule 71(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent application.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will not be public, will take place before the examining division

on 28.04.06 at 09.00 hrs at the EPO,
PschorrHöfe, Bayerstr. 34, D-80335 München

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 10/2000, 456).
If you do not appear as summoned, the oral proceedings may continue without you (R. 71(2) EPC).
Your attention is drawn to Rule 2 EPC, regarding the language of the oral proceedings, and to the OJ EPO 9/1991, 489, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (Rule 71a EPC), is 28.03.06.
The actual room number as well as the waiting room numbers will be given to you by the porter in the foyer at the above EPO address. Parking is available free of charge in the underground car park. However, this applies only in the case of accessing the car park via the entrance "Zollstrasse".

1st Examiner:
Kardas-Llorens E

2nd Member:
Smeets D

Chairman:
Couzy F

For the Examining Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Annexes:
Confirmation of receipt (Form 2936)
Communication (EPO Form 2906)

Registered letter with advice of delivery
EPO Form 2008 05.05 [ORAL03=9999] 13.12.05

to EPO postal service: 13.12.05

Bescheid/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum Date Date 20.12.2005	Blatt Sheet Feuille 1	Anmelde-Nr.: Application No.: Demande n°: 02 766 997.7

The examination is being carried out on the **following application documents:**

Description, Pages

1-8, 10-77 as published

9, 9a received on 25.10.2005 with letter of 21.10.2005

Claims, Numbers

1-29 received on 25.10.2005 with letter of 21.10.2005

Drawings, Sheets

1/34-34/34 as published

1. In response to the communication from the examining division dated 14.04.05 the applicant has filed with his reply dated 21.10.05 a set of claims 1-29 and amended description pages 9 a nd 9a.

2. **Objections raised in the prior communications, in particular concerning novelty, clarity and inventive step are still relevant for the subject-matter of present claims.**

3. Oral proceedings were requested for the case where the rejection of the application would be the intention of the examining division.
Thus, the applicant is summoned to oral proceedings.

4. In order to assist the applicant towards the objections of the examining division here are some comments to the above reply of the applicant:

-Clarity:
-The wording "stably associated";
On page 5, first paragraph, the applicant has stated that "stable association may be effected by direct bonding or encapsulation, such as a covalent bonding, non covalent bonding and trapping the agent in the interior of the delivery vehicle" (§ 0070).
This is also the understanding of the division, thus, according to this wording any kind of bonding is possible!.
-Contrary to applicants' opinion related to the decision T68/85 the division is of the opinion that said decision is not applicable to the present case and that the present invention can be defined in its claims by technical terms which clearly define the subject-matter and are not necessarily only functional.
-The wording "delivery vehicles";
(see applicant's comments in his above reply page 4)
As a suitable "delivery vehicle" in the present invention (see in particular § 0140) besides different kind of vehicles also tablets are meant. Therefore, an "association" with any kind of delivery vehicle is also aimed in the present invention.
-The wording of a first medical use claim according to claim 27, in particular the wording " for use in the treatment of a disease condition in a subject" will be discussed in the light of the Guidelines C-IV, 4.2.

the possibility of taking samples (Rule 28(3)), and there is thus no need to indicate another process for the production of the biological material.

4. Industrial application

4.1 General remarks

Art. 57

"An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture". "Industry" should be understood in its broad sense as including any physical activity of "technical character" (see IV, 1.2), i.e. an activity which belongs to the useful or practical arts as distinct from the aesthetic arts; it does not necessarily imply the use of a machine or the manufacture of an article and could cover e.g. a process for dispersing fog or for converting energy from one form to another. Thus, Art. 57 excludes from patentability very few "inventions" which are not already excluded by the list in Art. 52(2) (see IV, 2.1). One further class of "invention" which would be excluded, however, would be articles or processes alleged to operate in a manner clearly contrary to well-established physical laws, e.g. a perpetual motion machine. Objection could arise under Art. 57 only insofar as the claim specifies the intended function or purpose of the invention, but if, say, a perpetual motion machine is claimed merely as an article having a particular specified construction then objection should be made under Art. 83 (see II, 4.11).

4.2 Surgery, therapy and diagnostic methods

Art. 52(4)

"Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods." Hence, patents may be obtained for surgical, therapeutic or diagnostic instruments or apparatuses for use in such methods. The manufacture of prostheses or artificial limbs could be patentable. For instance, a method of manufacturing insoles in order to correct the posture or a method of manufacturing an artificial limb should be patentable. In both cases, taking the imprint of the footplate or a moulding of the stump on which an artificial limb is fitted is clearly not of a surgical nature and does not require the presence of a medically qualified person. Furthermore, the insoles as well as the artificial limb are manufactured outside the body. However, a method of manufacturing an endoprosthesis outside the body, but requiring a surgical step to be carried out for taking measurements, would be excluded from patentability under Art. 52(4) EPC (see T 1005/98, not published in OJ).

Art. 54(5)

Patents may also be obtained for new products for use in these methods of treatment or diagnosis, particularly substances or compositions. However, in the case of a known substance or composition, this may only be patented for use in these methods if the known substance or composition was not previously disclosed for use in surgery, therapy or diagnostic methods practised on the human or animal body (**"first medical use"**). The same substance or composition cannot subsequently be patented for any other use of that kind. A claim to a known substance or composition for the first use in surgical, therapeutic and/or diagnostic methods should be in a form such as: "Substance or composition X" followed by the indication of the use, for instance "... for use as a medicament", "... as an antibacterial agent " or "... for curing disease Y". In contrast to what is stated in general in III, 4.8, these types of claims will be regarded as restricted to the substance or composition when presented or packaged for the use. Art. 54(5) thus provides for an exception from the general principle that product claims can only be obtained for (absolutely) novel products. However, this does not mean that product claims for the first medical use need not fulfil all other requirements of patentability, especially that of inventive step (see T 128/82, OJ 4/1984, 164).

A claim in the form "Use of substance or composition X for the treatment of disease Y ..." will be regarded as relating to a method for treatment explicitly excluded from patentability by Art. 52(4) and therefore will not be accepted.

Art. 82

If an application discloses for the first time a number of distinct surgical, therapeutic or diagnostic uses for a known substance or composition, normally in the one application independent claims each directed to the substance or composition for one of the various uses may be allowed; i.e. an a priori objection of lack of unity of invention should not, as a general rule, be raised (see III, 7.6).

A claim in the form "Use of a substance or composition X for the manufacture of a medicament for therapeutic application Z" is allowable for either a first or "subsequent" (second or further) such application ("**second medical use**"-type of claim or "Swiss-type" claim), if this application is new and inventive (cf. G 5/83, OJ 3/1985, 64). The same applies to claims in the form "Method for manufacturing a medicament intended for therapeutic application Z, characterised in that the substance X is used" or the substantive equivalents thereof (see T 958/94, OJ 6/1997, 241). In cases where an applicant simultaneously discloses more than one "subsequent" therapeutic use, claims of the above type directed to these different uses are allowable in the one application, but only if they form a single general inventive concept (Art. 82). Regarding use or method claims of the above type, it should also be noted that a mere pharmaceutical effect does not necessarily imply a therapeutical application. For instance, the selective occupation of a specific receptor by a given substance cannot be considered in itself as a therapeutic application; indeed, the discovery that a substance selectively binds a receptor, even if representing an important piece of scientific knowledge, still needs to find an application in the form of a **defined, real** treatment of a pathological condition in order to make a technical contribution to the art and to be considered as an invention eligible for patent protection (see T 241/95, OJ 2/2001, 103). See also III, 4.14, for the functional definition of a pathological condition.

4.2.1 Limitations of exclusion under Art. 52(4)

Art. 52(4)

It should be noted that Art. 52(4) excludes only methods of treatment by surgery or therapy and diagnostic methods. It follows that other methods of treatment of live human beings or animals (e.g. treatment of a sheep in order to promote growth, to improve the quality of mutton or to increase the yield of wool) or other methods of measuring or recording characteristics of the human or animal body are patentable provided that (as would probably be the case) such methods are of a technical and not essentially biological character (see IV, 3.4) and are susceptible of industrial application. The latter proviso is particularly important in the case of human beings. For example, an application with a claim for a method of contraception, which is to be applied in the private and personal sphere of a human being, is not susceptible of industrial application (see T 74/93, OJ 10/1995, 712). However, an application containing claims directed to the purely cosmetic treatment of a human by administration of a chemical product is considered as being susceptible of industrial application (see T 144/83, OJ9/1986, 301). A cosmetic treatment involving surgery or therapy would, however, not be patentable (see below).

In order to be excluded, a treatment or diagnostic method must actually be carried out on the living human or animal body. A treatment of or diagnostic method practised on a dead human or animal body would therefore not be excluded from patentability by virtue of Art. 52(4). Treatment of body tissues or fluids after they have been removed from the human or animal body, or diagnostic methods applied thereon, are not excluded from patentability insofar as these tissues or fluids are not returned to the same body. Thus the treatment of blood for storage in a blood bank or diagnostic testing of blood samples is not excluded, whereas a treatment of blood by dialysis with the blood being returned to the same body would be excluded.

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BY FAX & COURIER

The European Patent Office
Erhardtstrasse 27
D-80469 Munich
Germany

21 October 2005

Dear Sirs

European Patent Application No. 02766997.7-2114
CELATOR TECHNOLOGIES INC.
Our Ref : N.91525 SER/LPC/ng

In response to the Communication from the Examining Division dated 14 April 2005, please amend the application as follows:

1. Replace claims pages 78 to 85 at present on file with new pages 78 to 85 provided herewith; and
2. Replace description page 9 at present on file with new pages 9 and 9a provided herewith.

In order to assist the Examiner in reviewing the amendments, we are also enclosing a copy of old claims pages 78 to 85 and description page 9 showing the changes in hand.

Amendments

We have amended claims 1 and 15 (old claim 17) so that they refer the biological effect being a cytotoxic or cytostatic effect on tumor cells; inhibition of endoxtoxin-mediated activation of macrophage; inhibition of degranulation, superoxide generation, or leukocyte migration of leukocytes; or inhibition of proliferation of endothelial or smooth musle cells. Basis for this is in old claim 2 and in paragraph [0096] on page 27, in particular lines 4-9, 15-18 and 26-28.

We have deleted old claims 2, 3, 5, 18, 27 and 31 and renumbered the remaining claims accordingly.

We have inserted new claims 14 and 26. Both these claims refer to the first agent being irinotecan

and the second agent being 5-FU or FUDR, or the first agent being cisplatin and the second agent being 5-FU or FUDR. Basis for these claims is in old claims 16 and 30 respectively.

We have amended claims 16 to 20 (old claims 19 to 23) to take account of the amendments made to claim 15 (old claim 17).

We have also amended the description for conformity with the amended claims.

Invention

Before dealing with the specific objections raised, it may be helpful to introduce the problem which the invention solves and how it goes about solving it.

We start from the premise that several things are known. This is summarized in paragraph [0011] on page 6 of the application as filed. Certain drugs in the treatment of cancer, especially, can exhibit synergistic, or at least non-antagonistic, effects when both are administered. There has been a great deal of experimentation of how to go about this – relative dosage, timing, *etc.* It is also recognized that, although drug A and drug B may be non-antagonistic when they contact a cell at a certain mole ratio (say 10:1), they actually become antagonistic when they contact a cell at a different ratio (say 1:1).

It is easy to control the ratio of the drugs as administered, but, in order to exert their effect, they must contact the target cell – *i.e.*, a solid tumor or a rapidly proliferating circulating cell. Because different drugs have different pharmacokinetics, the ratio at which they are administered will not be maintained at the time they contact the target cells or tissue.

Another problem is the fact that drugs that are non-antagonistic at a given ratio at one concentration may not be non-antagonistic at the same ratio, but a different concentration. Thus, by way of hypothetical, although drug A and drug B may be non-antagonistic at a mole ratio of 10:1 A:B when each is at a concentration of 100 μM, the same drugs at the same ratio may be antagonistic when each is at a concentration of, say, 10 μM. It is also known that the concentration of drugs supplied to the patient is not the concentration of drugs that actually arrive at the target tissue.

Thus, the problem is to assure that, *when the drug compositions contact the target tissue*, the concentrations *and* the mole ratio of the drugs are such that they behave in a non-antagonistic manner. The invention solves this problem by taking two basic precautions:

> First, it provides that the therapeutic agents are stably associated with (coupled to) particulate delivery vehicles, because then the particulate delivery vehicles will control the pharmacokinetics, in particular by maintaining the same ratio of the drugs that was administered.

Second, the invention solves the problem of variability of non-antagonistic ratio with concentration by selecting ratios that maintain their non-antagonism over a wide range of concentrations.

Turning, therefore, to claim 1, the claim requires that both the first therapeutic agent and the second therapeutic agent be associated with particulate delivery vehicles. Second, it requires that the non-antagonistic biologic effect be maintained over a specific range of concentrations. The numbers in the claim refer to a particular form of expressing this stability of effect with concentration. The overall concentration range at which the agents affect >1% of cells will be extremely broad since only a few cells need to be affected. The claim requires that the mole ratio exhibit a non-antagonistic effect over at least 5% of this broad concentration range. Hence, the claim requires that the mole ratio of agents maintains their non-antagonism over a wide range of concentrations. As discussed in more detail below, the subject matter of claim 1 is both novel and inventive over the prior art.

International Preliminary Examination Report (Item 1)

The Examiner refers us to the International Preliminary Examination Report (IPER) that was raised on the International application from which the present application was derived (International Application No. PCT/CA02/01500; Published as WO 03/028696). We will deal with the objections in the order in which they rise in that report.

Methods of Treatment (Item III)

Old claims 41 to 48 were redrafted as first medical use claims upon entry to the European Regional Phase. These claims correspond to claims 27 to 29 filed herewith. As a result, the claims no longer refer to methods of therapeutic treatment carried out on the human or animal body.

Novelty and Inventive Step (Item V)

Novelty

Under Item V of the IPER, the Examiner suggests that the invention is not new in view of D1, D2, and D7. However, we submit that the present invention is novel over these documents. None of D1, D2 or D7 teach or suggest stably associating a combination of agents with a particulate delivery vehicle and selecting a mole ratio of agents that maintains their non- antagonism over a wide range of concentrations to ensure that they have a non-antagonistic effect at the target tissue.

Even if the comment that certain limitations "are worded in functional terms (results to be achieved) and are disregarded when determining novelty" is accepted – which it is not, as will be explained below – these cited documents do not destroy novelty. Distinction can be made simply based on the requirement that both the first and second therapeutic agents are stably associated with a particulate

delivery vehicle. None of D1, D2 or D7 disclose stable association of two agents with a particulate delivery vehicle.

The first cited document, D7: Stevenson, J. P. *et al.*, Oncology (2000) 14:91-92, describes a Phase I clinical trial using intravenous administration of irinotecan and UFT (uracil and tegafur) along with an oral dose of leucovorin. The IPER states that since the leucovorin dosage is oral, "an implicit particle delivery vehicle might be disclosed in some oral forms" such as the oral leucovorin which might be a tablet. According to the Physician's Desk Reference (PDR), leucovorin tablets do exist. However, the leucovorin is not stably associated with any particles in the tablet. It is merely mixed into the solid composition. In any event, there is only one active ingredient in the tablet. Neither the requirement for stable association nor the requirement that at least two agents be associated with a delivery vehicle is met.

The second document, D1: Guichard, S. *et al.*, Biochemical Pharmacology (1998) 55:667-676, is also cited as disclosing "compositions comprising particle delivery vehicles with the first and second therapeutic agent." This is simply not true. This document describes studies on cell cultures where combinations of drugs are administered to explore their cellular interaction. The drugs are administered in solution, not in the presence of any particulate delivery vehicles. Therefore, there are no compositions that reflect these drugs stably associated with delivery vehicles. They are at best associated with particles (not delivery vehicles) in that, <u>after</u> they are taken up by the cells, they are formed into complexes with protein or DNA. However, these are clearly not delivery vehicles, since the drugs have already been delivered.

The last document mentioned as putatively destroying novelty is D2: Thigpen, T., Seminars in Oncology (2002) 29: 11-16. This document was published subsequent to the priority dates to which the present application is entitled, and thus is not properly citable. In any case, the theme of the article is to explore the effects of new combinations of agents with what seems to be regarded as standard therapy with paclitaxel or platinum compounds. Among the drugs proposed to be combined is liposome-encapsulated doxorubicin. However, this is the <u>only</u> liposome associated drug in the study. Thus, the description in D2 does not include an instance where <u>at least two</u> therapeutic agents are stably associated with a delivery vehicle.

Thus, it is apparent that the claims are novel over the three documents referred to in the IPER.

The IPER does acknowledge the novelty of claims 21 and 22 then pending which are directed to methods to prepare compositions by predetermining non-antagonistic ratios as well as compositions prepared by these methods. As claims 23 to 37 are dependent ultimately on these claims, acknowledgment of novelty of these claims is also implied. Thus it is clear that the IPER acknowledges at least novelty of claims 21 to 40, which correspond to claims 15 to 26 filed herewith.

In the latest Examination Report, the Examiner objects to the clarity of the term "stably associated". However, we submit that this term is clear to the person skilled in the art. The term means that both the first and second agents are associated with the particulate delivery vehicle in a stable manner. The stable association may be effected by direct bonding or encapsulation, such as covalent bonding, non covalent bonding and trapping the agent in the interior of the delivery vehicle (paragraph [0070]).

Returning, now, to the question of whether the additional limitation in claim 1 is merely functional and to be discounted, we submit that the requirement that

> "[a] mole ratio of the first agent to the second agent which exhibits a non-antagonistic biological effect to relevant cells in culture or a cell-free system over at least 5% of such concentration range where more than 1% of the cells are affected ($f_a > 0.01$) in an *in vitro* assay for said biological effect, wherein said biological effect is
>
> > a cytotoxic or cytostatic effect on tumor cells; or
> >
> > inhibition of endotoxin-mediated activiation of macrophage; or
> >
> > inhibition of degranulation, superoxide generation, or leukocyte migration of leukocytes;
> >
> > or inhibition of proliferation of endothelial or smooth muscle cells"

is an allowable definition that limits the scope of the claim.

According to Decision T68/85 (Synergistic Herbicides/Ciba-Geigy) of the Boards of Appeal of the EPO and Section C-III 4.7 of the Guidelines for Examination of the EPO, subject matter can be defined functionally by result to be achieved if (i) the invention can only be defined in such terms or cannot otherwise be defined more precisely without unduly restricting the scope of the claims and (ii) the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation.

The subject matter of claim 1 satisfies both these criteria. Firstly, the claim refers to a mole ratio of the first agent to the second agent which exhibits a non-antagonistic biological effect over a specific concentration range. The mole ratio can only be defined in such terms because it will differ between different combinations of the first and second agents. Introduction of specific ratios is inappropriate and would unduly restrict the scope of protection afforded the applicant.

Secondly, the application as filed provides considerable detail regarding how the non-antagonistic mole ratio can be determined (paragraphs [0081] to [0100] on pages 22 to 30). These methods are also disclosed in the Examples. Such methods are straightforward for the person skilled in the art and do not require undue experimentation or inventive skill. As a result, the functional limitation in claim 1 is allowable and should be considered when determining novelty.

In summary, the mole ratio in claim 1 can only be defined in such terms and cannot otherwise be defined more precisely without unduly restricting the scope of the claims because, as is apparent, the precise mole ratio will differ for different combinations of agents. However, the application as filed describes in detail over 9 pages exactly how to determine the mole ratio. It is therefore routine for a person skilled in the art to identify the mole ratio as defined in the claim.

As discussed above claim 1 is novel over D1, D2 and D7 even if the functional limitation is disregarded. However, the subject matter of claim 1 can be further distinguished from the subject matter disclosed in those documents on the basis of the mole ratio defined therein. None of D1, D2 or D7 disclose a mole ratio which exhibits a non-antagonistic biological effect over such a concentration range as defined in claim 1.

Overall, we submit that all of the claims of the present application are novel over the prior art.

Inventive step

The IPER states that all claims are lacking inventive step because "compositions comprising therapeutic agents with synergistic or additive biologic effects are taught by known prior art". The Applicant has acknowledged that synergistic or addictive effects of agents are known in the art. However, as discussed above, the invention concerns ensuring that agents contact the target tissue at a concentration and mole ratio that allows them to behave in a non-antagonistic manner.

The invention solves this problem by stably associating the agents with particulate delivery vehicles and selecting a ratio that maintains their non-antagonism over a wide range of concentrations. The invention offers for the first time a simple *in vitro* assay that ensures that a combination of agents will have a non-antagonistic effect at the target tissue. Before the invention, it was necessary to determine a suitable mole ratio and concentration of agents using trial and error in animal models or human patients.

It should be apparent that the very long history of attempts to employ combinations of drugs successfully without arriving at the advantageous solution described by the inventors is evidence of inventive step. Over all the times that combinations of drugs have been employed, no one has proposed controlling their pharmacokinetics by attaching them to particulate delivery vehicles that themselves control the pharmacokinetics or ensuring that the ratio administered is such that non-antagonism will be maintained over a wide range of concentrations. There is no cited art whatsoever that makes either of these suggestions.

As a result, it would not have been obvious for a person skilled in the art to stably associate a combination of agents with delivery vehicles and to select ratios that maintain their non-antagonism over a wide range of concentrations in order to assure that, when the drug compositions contact the target tissue, the concentrations and the mole ratio of the drugs are such that they behave in a non-antagonistic manner. The present claims therefore comprise an inventive step.

Other Objections (Item 2)

Clarity

In the International Search Report, the Examiner objects that independent claims 1 and 15 (old claim 17)lack clarity because they refer to an extremely large number of possible agents. We submit that these claims are clear to a person skilled in the art. Nevertheless, in order to facilitate examination, we have amended claims 1 and 15 to define the non-antagonistic biological effect exhibited by the first and second agents. As will be appreciated from the discussion above, the definitions of the biological effect are linked as to form a single general inventive concept.

The Examiner also objects to the functional definition of subject matter in claim 1. The clarity of this definition has been dealt with above in the section concerning novelty. As discussed therein, the functional definition is allowable in accordance with the criteria established by the Boards of Appeal of the EPO.

Rule 29(2) EPC

The claims filed herewith include one independent composition claim (claim 1), one independent method claim (claim 15) and one first medical use claim (claim 27). As a result, the Examiner's objection under Rule 29(2) EPC is no longer applicable.

The application is believed to be in allowable form and the Examiner is asked to reconsider it favourably. If however there are any queries outstanding, please issue a further examination report or telephone. Only as a precaution in case the Examiner is minded to reject the application, we request Oral Proceedings.

Also, we request that the Examiner telephones me or issues a further examination report if the Examining Division is minded to issue a Communication under Rule 51(4) EPC but wishes to propose amendments to the claims. The Applicant does not consent to modifications being made to the claims by the Examining Division without permission from the Applicant, in view of the potential difficulties that such unapproved amendments to the claims can cause an Applicant under the Rule 51(4) procedure in force from 1 July 2002.

Please acknowledge receipt of this letter by stamping and returning the copy letter provided.

Yours faithfully

SARAH E. ROQUES

Claims

1. A composition which comprises delivery vehicles, said delivery vehicles being particles of sizes dependent on the routes of administration having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio of the first agent to the second agent which exhibits a non-antagonistic biological effect to relevant cells in culture or a cell-free system over at least 5% of the concentration range where > 1% of the cells are affected ($f_a > 0.01$) in an *in vitro* assay for said biological effect, wherein said biological effect is

a cytotoxic or cytostatic effect on tumor cells; or

inhibition of endotoxin-mediated activiation of macrophage; or

inhibition of degranulation, superoxide generation, or leukocyte migration of leukocytes; or

inhibition of proliferation of endothelial or smooth muscle cells.

2. The composition of claim 1 wherein said agents are antineoplastic agents.

3. The composition of claim 1 or 2 wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

4. The composition of claim 3 wherein said vehicles have a mean diameter of less than 250 nm.

5. The composition of any of claims 1 to 4 wherein said delivery vehicles comprise

liposomes, and/or

lipid micelles, and/or

block copolymer micelles, and/or

microparticles, and/or

nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

6. The composition of any one of claims 1 to 5 wherein said first and second agents are co-encapsulated.

7. The composition of any of claims 1 to 6 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1 - 0.9) in said *in vitro* assay.

8. The composition of claim 7 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2 - 0.8) in said *in vitro* assay.

9. The composition of claim 8 wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

10. The composition of any of claims 1 to 9 which, when administered to a subject, provides a therapeutic activity greater than that which is obtained when said agents are administered in the same ratio but not stably associated with delivery vehicles.

11. The composition of any one of claims 1 to 10 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a

mitochondrial poison, a signal transduction inhibitor and an immunoagent.

12. The composition of claim 11 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2 - or a G_2/M- checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

13. The composition of claim 12

wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-

FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

14. The composition of claim 13 wherein the first agent is irinotecan and the second agent is 5-FU or FUDR or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR.

15. A method to prepare a composition of claim 1, which method comprises

a) determining in a relevant cell culture assay or cell-free assay for biological activity a mole ratio of said first and second agent which is non-

antagonistic over at least 5% of the concentration range over which greater than 1% of cells are affected ($f_a > 0.01$) by said ratio of agents, and

b) encapsulating with said delivery vehicles a mole ratio of agents determined to be non-antagonistic in step a), wherein said biological effect is

a cytotoxic or cytostatic effect on tumor cells; or

inhibition of endotoxin-mediated activiation of macrophage; or

inhibition of degranulation, superoxide generation, or leukocyte migration of leukocytes; or

inhibition of proliferation of endothelial or smooth muscle cells.

16. The method of claim 15 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 1% - 99% of the cells are affected ($f_a = 0.01 - 0.99$) in said *in vitro* assay.

17. The method of claim 16 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that >1% of the cells are affected ($f_a > 0.01$) in said *in vitro* assay.

18. The method of claim 17 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10 - 90% of the cells are affected ($f_a = 0.1 - 0.9$) in said *in vitro* assay.

19. The method of claim 18 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20 - 80% of the cells are affected ($f_a = 0.2 - 0.8$) in said *in vitro* assay.

20. The method of claim 19 wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20 - 80% of the cells are affected in said *in vitro* assay.

21. The method of any of claims 15 to 20, wherein said determining employs testing at least one ratio of said agents at a multiplicity of concentrations and applying an algorithm to calculate a synergistic, additive, or antagonistic effect for said ratio over a range of concentrations.

22. The method of claim 21 which employs testing a multiplicity of ratios, and wherein said algorithm is the Chou-Talalay median effect method.

23. The method of any of claims 15 to 22 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

24. The method of claim 23 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M- checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

25. The method of claim 24

wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is adriamycin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

26. The method of claim 25 wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin and the second agent is 5-FU or FUDR.

27. A composition according to any one of claims 1 to 16, for use in the treatment of a disease condition in a subject.

28. The composition of claim 27 wherein the subject is a human.

29. The composition of claim 27 wherein the subject is a non-human mammal or avian.

additivity over a range of concentrations. Preferably, the CI is synergistic over a wide concentration range. Preferred agents are antitumor agents. Any method which results in determination of a ratio of agents which maintains a non-antagonistic effect over a desired range of concentrations may be used.

[0021] More particularly, the invention relates to a composition which comprises delivery vehicles, said delivery vehicles being particles of sizes dependent on the routes of administration having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio of the first agent to the second agent which exhibits a non-antagonistic biological effect to relevant cells in culture or a cell-free system over at least 5% of the concentration range where > 1% of the cells are affected ($f_a > 0.01$) in an *in vitro* assay for said biological effect, wherein said biological effect is a cytotoxic or cytostatic effect on tumor cells; or inhibition of endotoxin-mediated activiation of macrophage; or inhibition of degranulation, superoxide generation, or leukocyte migration of leukocytes; or inhibition of proliferation of endothelial or smooth muscle cells. In one embodiment, said agents are antineoplastic agents. By "relevant" cells, applicants refer to at least one cell culture or cell line which is appropriate for testing the desired biological effect. For example, if the agent is an antioneoplastic agent, a "relevant" cell would be a cell line identified by the Development Therapeutics Program (DTP) of the National Cancer Institute (NCI)/National Institutes of Health (NIH) as useful in their anticancer drug discovery program. Currently the DTP screen utilizes 60 different human tumor cell lines. The desired activity on at least one of such lines would need to be demonstrated.

[0022] The compositions of the invention are used to deliver a synergistic or additive ratio of two or more therapeutic agents to a desired target by administering the compositions of the invention.

[0023] In another aspect, the invention is directed to a method to prepare a composition of the invention, which method comprises a) determining in a relevant cell culture assay or cell-free assay for biological activity a mole ratio of said first and second agent which is non-antagonistic over at least 5% of the concentration range over which greater than 1% of cells are affected ($f_a > 0.01$) by said ratio of agents,

and b) encapsulating with said delivery vehicles a mole ratio of agents determined to be non-antagonistic in step a), wherein said biological effect is a cytotoxic or cytostatic effect on tumor cells; or inhibition of endotoxin-mediated activiation of macrophage; or inhibition of degranulation, superoxide generation, or leukocyte migration of leukocytes; or inhibition of proliferation of endothelial or smooth muscle cells. The method may comprise providing a panel of at least two therapeutic agents wherein the panel comprises at least one, but preferably a multiplicity of ratios of said agents, testing the ability of the members of the panel to exert a biological effect on a relevant cell culture or cell-free system over a range of concentrations, selecting a member of the panel wherein the ratio provides a synergistic or additive effect on said cell culture or cell-free.

Claims

1. A composition which comprises delivery vehicles, said delivery vehicles being particles of sizes dependent on the routes of administration having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio of the first agent to the second agent which exhibits a non-antagonistic biological effect to relevant cells in culture or a cell-free system over at least 5% of ~~such~~ the concentration range where > 1% of the cells are affected ($f_a > 0.01$) in an *in vitro* assay for biological effect,

~~2. A composition which comprises delivery vehicles, being particles of sizes dependent on the routes of administration said delivery vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio of the first agent to the second agent which exhibits a non-antagonistic~~ cytotoxic or cytostatic ~~or biological effect to relevant cells wherein said agents are antineoplastic agents.~~

~~3. The composition of claim 2 wherein said non-antagonistic effect is~~ exhibited over at least ~~5% of the~~ concentration range where > 1% of relevant cells are ~~affected ($f_a > 0.01$) in an *in vitro* assay for cytotoxicity.~~

2 ~~4~~. The composition of claim 1 wherein said agents are antineoplastic agents.

~~5. The composition of claim 1 wherein the composition comprises a third~~ agent.

3 ~~6~~. The composition of claim 1 or 2 wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

(A) wherein said biological effect is a effect on tumor cells; or inhibition of endotoxin-mediated activation of macrophage; or inhibition of degranulation, superoxide generation, or leukocyte migration of leukocytes; or inhibition of proliferation of endothelial or smooth muscle cells.

(Basis: page 27, lines 4-9, 15-18 and 26-28)

4 ~~4~~. The composition of claim 3 wherein said vehicles have a mean diameter of less than 250 nm.

5 ~~8~~. The composition of any of claim 1 -4 ~~or 2~~ wherein said delivery vehicles comprise

liposomes, and/or
lipid micelles, and/or
block copolymer micelles, and/or
microparticles, and/or
nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

6 ~~9~~. The composition of any of claim 1 -5 wherein said first and second agents are co-encapsulated.

7 ~~10~~. The composition of any of claim 1 -6 ~~or claim 9~~ wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1 - 0.9) in said *in vitro* assay.

8 ~~11~~. The composition of claim 7 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2 - 0.8) in said *in vitro* assay.

9 ~~12~~. The composition of claim 8 wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

10 ~~13~~. The composition of any of claim 1 -9 ~~or claim 2~~ which, when administered to a subject, provides a therapeutic activity greater than that which is obtained when said

agents are administered in the same ratio but not stably associated with delivery vehicles.

any of 5 1-10

11 14. The composition of claim 12 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

11

12 15. The composition of claim 14 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2 - or a G_2/M- checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a

cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

13 ~~16~~. The composition of claim 12

wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

14. The composition of claim 13 wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR.

(basis: old claim 16 above)

15 ~~17~~. A method to prepare a composition of claim 1 ~~comprising delivery vehicles, said vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio which is non-antagonistic~~, which method comprises

a) determining in a relevant cell culture assay or cell-free assay for biological activity a mole ratio of said first and second agent which is non-antagonistic over at least 5% of the concentration range over which greater than 1% of cells are affected ($f_a > 0.01$) by said ratio of agents, and

b) encapsulating with said delivery vehicles a mole ratio of agents determined to be non-antagonistic in step a), (A) (see old page 78)

~~18. A method to prepare a composition comprising drug delivery vehicles, said vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio which is non-antagonistic, which method comprises~~

~~a) determining in a relevant cell culture assay or cell-free assay a mole ratio of said first and second agent which is non antagonistic, wherein said agents are antineoplastic agents, and~~

~~b) encapsulating with said delivery vehicles a mole ratio of agents determined to be non-antagonistic in step a).~~

16 ~~19~~. The method of claim 15 ~~17~~ wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 1% - 99% of the cells are affected ($f_a = 0.01 - 0.99$) in ~~an~~ said *in vitro* assay ~~for cytotoxicity or cytostatis~~.

17 ~~20~~. The method of claim 16 ~~18~~ wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that >1% of the cells are affected ($f_a > 0.01$) in ~~an~~ said *in vitro* assay ~~for cytotoxicity or cytostatis~~

18 ~~21~~. The method of claim 17 ~~19 or claim 20~~ wherein said non-antagonistic

effect is exhibited over at least 5% of the concentration range such that 10 - 90% of the cells are affected (f_a = 0.1 - 0.9) in ~~an~~ said *in vitro* assay ~~for cytotoxicity or cytostatic~~.

19 ~~22~~. The method of claim ~~21~~ 18 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20 - 80% of the cells are affected (f_a = 0.2 - 0.8) in ~~an~~ said *in vitro* assay ~~for cytotoxicity or cytostatic~~

20 ~~23~~. The method of claim ~~22~~ 19 wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20 - 80% of the cells are affected in ~~an~~ said *in vitro* assay ~~for cytotoxicity or cytostatic~~

21 ~~24~~. The method of ~~claim 17~~ any of claims 15-20, wherein said determining employs testing at least one ratio of said agents at a multiplicity of concentrations and applying an algorithm to calculate a synergistic, additive, or antagonistic effect for said ratio over a range of concentrations.

22 ~~25~~. The method of claim ~~24~~ 21 which employs testing a multiplicity of ratios, and

~~26. The method of claim 24~~ wherein said algorithm is the Chou-Talalay median effect method.

~~27. The method of claim 24 wherein said agents are antineoplastic agents.~~

23 ~~28~~. The method of ~~claim 18~~ any of claims 15-22 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

24 23
29. The method of claim 18 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2 - or a G_2/M- checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

25 24
25 30. The method of claim 20

wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR,

or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is adriamycin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

~~31. A composition prepared by the method of any one of claims 17 to 30.~~

27 ~~32~~. A composition according to any one of claims 1 to 16 ~~or 31~~, for use in the treatment of a disease condition in a subject.

28 ~~33~~. The composition of claim 27 ~~32~~ wherein the subject is a human.

29 ~~34~~. The composition of claim 27 ~~32~~ wherein the subject is a non-human mammal or avian.

26. The method of claim 25 wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or
wherein the first agent is cisplatin and the second agent is 5-FU or FUDR.
(Basis: old claim 30 above).

additivity over a range of concentrations. Preferably the CI is synergistic over a wide concentration range. Preferred agents are antitumor agents. Any method which results in determination of a ratio of agents which maintains a non-antagonistic effect over a desired range of concentrations may be used.

[0021] More particularly, the invention relates to a composition which comprises delivery vehicles, said delivery vehicles ~~having encapsulated therein at least a first~~ <as in claim 1>. therapeutic agent and a second therapeutic agent in a mole ratio of the ~~first~~ agent to the second agent which exhibits a non-antagonistic biologic ~~effect~~ to relevant cells in culture or cell-free system over at least 5% of such concentration range where greater than 1% of the cells are affected (Fraction ~~affected~~ (f_a) > 0.01) or to a composition which comprises delivery vehicles, ~~said~~ delivery vehicles having encapsulated therein at least a first therapeutic agent and a second therapeutic agent in a mole ratio of the first agent to the ~~second agent which exhibits a non-antagonistic cytotoxic effect or cytostatic effect to relevant cells wherein~~ In one embodiment, said agents are antineoplastic agents. By "relevant" cells, applicants refer to at least one cell culture or cell line which is appropriate for testing the desired biological effect. For example, if the agent is an antineoplastic agent, a "relevant" cell would be a cell line identified by the Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI)/National Institutes of Health (NIH) as useful in their anticancer drug discovery program. Currently the DTP screen utilizes 60 different human tumor cell lines. The desired activity on at least one of such cell lines would need to be demonstrated.

[0022] ~~In another aspect,~~ The invention ~~is directed to a method~~ compositions of the are used to deliver a synergistic or additive ratio of two or more therapeutic agents to a desired target by administering the compositions of the invention.

[0023] In another aspect, the invention is directed to a method to prepare a ~~therapeutic~~ composition of the invention, which method comprises <as claim 15>. ~~comprising delivery vehicles, said delivery vehicles containing a ratio of at least two therapeutic agents which is non-antagonistic over a range of concentrations which~~ The method may comprise providing a panel of at least two therapeutic agents wherein the panel comprises at least one, but preferably a multiplicity of ratios of said agents, testing the ability of the members of the panel to exert a biological effect on a relevant cell culture or cell-free system over a range of concentrations, selecting a member of the panel wherein the ratio provides a synergistic or additive effect on said cell culture or cell-free

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Application No.	Ref.	Date
02 766 997.7 - 2114	N.91525SER	14.04.2005
Applicant: Celator Technologies Inc.		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

Kardas-Llorens, E
Primary Examiner
for the Examining Division

Enclosure(s): 2 page/s reasons (Form 2906)

FA=4/20/05

Registered Letter
EPO Form 2001 07.02CSX

The examination is being carried out on the **following application documents**:

Description, Pages

1-77 as published

Claims, Numbers

1-34 received on 16.04.2004 with letter of 15.04.2004

Drawings, Sheets

1/34-34/34 as published

1. An international preliminary examination report has already been drawn up for the present application in accordance with the PCT. The deficiencies mentioned in that report (in particular objections under item V) give rise to objections under the corresponding provisions of the EPC.

2. Furthermore, the following should be considered:
-Clarity (Art. 84 EPC):
The objections raised in the PCT/ISA/210 are valid when considering the wording of present claims.

-Rule 29(2) EPC, Guidelines C III, 3.2, **3.3**:
The number of independent claims should be limited to one independent claim in each category.

Novelty (Art. 54 EPC), Inventive Step (Art. 56 EPC):
As far as applicant's comments in his reply dated 25.02.04 is concerned the following

should be considered. The subject-matter of independent claim 1 is directed to a composition. For purposes of novelty, only the specific technical features in said claim can be taken in account. The wording "stably associated" in said claim is not concise and does not constitute a technical feature for purposes of determining novelty (Guidelines C III, 4.1, 4.2, 4.4-4.5a, 4.7a, Decision T94/82).

Moreover, in said above reply it is argued that "the invention lies in assuring that the synergistic or additive ratios are maintained in a subject by allowing the pharmacokinetics of delivery vehicles to control the pharmacokinetics of these components".
The effects of combinations of drugs which lead to synergistic effects are already obvious for skilled persons in the art. This has also been acknowledged in the present description paragraphs (0004) to (0018). Another further aspect is that the present independent claims are directed to any kind of "first" and "second therapeutic agent". Thus, it is doubtful that any kind of therapeutic agent in combination can lead to synergistic effects.

3. In view of the above objections it is not at present practicable to carry out a full examination of the application. The applicant is therefore requested to file suitable amendments upon which the further prosecution of the application is to be based.

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BY COURIER

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26 October 2004

Dear Sirs

European Patent Application No. 02766997.7-2114
CELATOR TECHNOLOGIES, INC.
Our Ref : N.91525 SER/mr

Further to the Communication issued 17 June 2004, we have now been advised of the correct address for the inventor Clifford Shew. The correct is :

Suite # 2205, 1188 Howe Street
Vancouver, BC
Canada
V6Z 2S8

We request that the European Patent Office register be updated to reflect the correct address for the inventor Clifford Shew.

Please acknowledge receipt of this letter by date stamping and returning the enclosed acknowledgement copy.

Yours faithfully

SARAH E. ROQUES